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10/571,184	07/17/2006	David Morton	478.1077	9629

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EXAMINER	
OLSON, ERIC	
ART UNIT	PAPER NUMBER
1623	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/571,184	MORTON ET AL.	
	Examiner	Art Unit	
	ERIC S. OLSON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-11,13-28 and 30-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-11,13-28 and 30-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 18, 2009 has been entered.

Detailed Action

This office action is a response to applicant's communication submitted September 18, 2009 wherein claims 1 and 17 are amended and new claims 47 and 48 are introduced. This application is a national stage application of PCT/GB04/03932, filed September 15, 2004, which claims priority to foreign applications GB0321611.1, filed September 15, 2003, and GB0327723.3, filed November 28, 2003.

Claims 1-3, 6-11, 13-28, and 30-48 are pending in this application.

Claims 1-3, 6-11, 13-28, and 30-48 as amended are examined on the merits herein.

The following new grounds of rejection are introduced:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims recite the abbreviation MMAD without ever defining what the abbreviation stands for. Therefore the claims are indefinite.

The following rejections of record in the previous action are maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 6-10, 14-28, 30 , 40-42, and 44-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ahmed et al. (PCT international publication

WO99/06025, reference of record in previous action) in view of Staniforth. (PCT international publication WO97/03649, of record in previous action)

Ahmed et al. discloses a method of treating conditions characterized by late phase allergic reactions (e.g. late phase asthma) by administering an ultra-low molecular weight heparin, or ULMWH. (p. 6 line 14 – p. 7 line 15) Because the composition is able to diminish bronchial hyper-reactivity after antigen challenge to the patient. (p. 7 lines 1-4) one of ordinary skill in the art would see it as being useful for treating an acute asthma attack. The ULMWH has little or no anticoagulant activity and is administered as a pharmaceutical composition which is an inhalable powder. (p. 7 lines 16-21) Besides ULMWH, the inhalable compositions can also comprise other sulfated polysaccharides such as dermatan sulfate, chondroitin sulfate, pentosan polysulfate and/or other glycosaminoglycans and mucopolysaccharides. (p. 20 lines 1-10) Suitable powder compositions include compositions of heparin intermixed with inert powders such as lactose and delivered through an inhaler device. (p. 21 lines 14-19) Other claimed properties of the powder, namely its utility in certain therapeutic indications as recited in claims 25-28, are present in these pharmaceutical compositions, as they are identical to those disclosed in the instant specification to be useful for treating these diseases. Ahmed et al. does not disclose compositions comprising the specific particle sizes or additives included in the aforementioned claims, or a method comprising spray drying said composition.

Staniforth discloses a powder for use in a dry powder inhaler comprising an active material and an anti-adherent material, where the active material makes up at

least 60% of the weight of the powder. (p. 4 lines 6-11) The active material used in these compositions can be a carbohydrate, for example heparin. (p. 11 lines 21-22) Anti-adherent materials can include additives such as leucine, an amino acid, or lecithin, a phospholipid, which are force control agents according to the limits of the instant claims, and additional additives such as lactose. (p. 5 line 32 – p. 6 line 9) N-acetyl-L-cysteine is another additive that can be used. (p. 9 lines 34-37) In a preferred embodiment at least 90% of the composition is made up of particles of active agent (fine particles) which have a diameter of about 0.1-5 μm. (p. 8 lines 26-36) Example 1 discloses a dry powder mixture wherein the active agent particles have a MMAD of 2.1 μm with about 1% leucine by weight. (p. 18 lines 1-21) However, according to p. 13 line 13 - p. 14 line 3 of the specification, additives (e.g. leucine and/or N-acetylcysteine) can make up 0.1-40%, preferably 0.25-5% of the weight of the composition. The optimal size for the agglomerates of active agent and carrier particles is at least 45 μm, indicating that it is preferable to use carrier particles of at least 45 μm. (p. 5 lines 11-27)

It would have been obvious to one of ordinary skill in the art at the time of the invention to make a powder composition of ULMWH of the type described by Ahmed et al. incorporating anti-adherent particles as described by Staniforth, and to use the composition for treating late-phase asthma. One of ordinary skill in the art at the time of the invention would have been motivated to incorporate the anti-adherent particles described by Staniforth because Staniforth discloses that the anti-adherent particles improve delivery of active agents by inhalation. One of ordinary skill in the art would

have reasonably expected success because Staniforth discloses that these methods can be used to formulate inhalable powders for the delivery of heparin.

Furthermore, with respect to the specific particle size of claim 23 or composition of claim 43, one of ordinary skill in the art would have recognized that the disclosure of Staniforth covers a broad range of particle sizes and compositions, and would have been able to adjust the specific amounts with in the disclosed ranges to arrive at the optimal value within the prior art disclosure. Doing so is well within the ordinary and routine level of skill in the art.

With respect to the amount of additive (e.g. leucine or N-acetylcysteine) it would have been obvious to one of ordinary skill in the art to use 2% or more, for example 2-5% of the additive, in the compositions. One of ordinary skill in the art would have easily and routinely been able to optimize the amount of additive present in order to prepare the composition according to the prior art description.

Therefore the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted September 18, 2009, with respect to the above ground of rejection, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that the prior art teaches away from using an amino acid in an amount greater than 1%. However, according to MPEP 2123, disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. See In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not

become patentable simply because it has been described as somewhat inferior to some other product for the same use." See In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994) 27 F.3d at 554, 31 USPQ2d at 1132.). 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). Also, although Staniforth et al. discloses that compositions containing 5% or more of leucine have a decreased respirable fraction, there are no experimental results for other additives such as N-acetylcysteine. Still further, a specific example (example 3 on pp. 18-19) contains 2% leucine, indicating that amounts greater than 1% but lest than 5% are considered to be usable embodiments of the invention. Therefore compositions of 2% or greater of an amino acid are still considered to be obvious over the prior art.

Applicant further argues that the results presented in tables 2-3 on pp. 45-46 of the specification demonstrate unexpectedly improved fine particle fraction for the combination of heparin and leucine with percentages of leucine of 2% or more. However, according to MPEP 716.02(d), whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. In re Clemens, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980) See also In re Peterson, 315 F.3d 1325, 1329-31, 65 USPQ2d 1379, 1382-85 (Fed. Cir. 2003); In re Grasselli, 713 F.2d 731, 741, 218USPQ 769, 777 (Fed. Cir. 1983) The results indicated by Applicant only concern a single synergistic combination, heparin and leucine. They

therefore do not serve to demonstrate unexpected results for either the full scope of glycosaminoglycans (e.g. chondroitin sulfate, dermatan sulfate, hyaluronic acid) or the full scope of amino acids. (e.g. the 19 other canonical amino acids, as well as nonstandard amino acids such as carnitine, ornithine, or p-aminobenzoic acid)

For these reasons the rejection is deemed proper and maintained.

Claims 31-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ahmed et al. (PCT international publication WO99/06025, reference of record in previous action) in view of Staniforth (PCT international publication WO97/03649, of record in previous action) as applied to claims -3, 6-10, 14-30 , 40-42, and 44-48 above, and further in view of Dunbar et al. (Reference included with PTO-892)

The disclosure of Ahmed et al. in view of Staniforth is discussed above. Ahmed et al. in view of Staniforth does not disclose a method wherein the particles of heparin are spray dried at a controlled velocity of less than 20 m/s or one where the droplets are generated by an ultrasonic nebuliser.

Dunbar et al. discloses a method of spray drying that can be used to form dry powder aerosol formulations for inhalation, using either an ultrasonic nebuliser or an airblast nebuliser. (p. 434, left column paragraphs 1-2) The droplet velocities produced by the ultrasonic nebuliser ranged from 0.47-1.09 m/s. (p. 436, right column last paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to make the powders as taught by Ahmed et al. in view of Staniforth by spray

drying using an ultrasonic nebuliser. One of ordinary skill in the art would have been motivated to make the particles by this method because Dunbar et al. discloses that spray drying using an ultrasonic nebuliser is a suitable method for making inhalable dry powders having the required properties. One of ordinary skill in the art would reasonably have expected success because spray drying is a common and well-characterized method of making pharmaceutical powder formulations.

Therefore the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted September 18, 2009, with respect to the above ground of rejection, have been fully considered and not found to be persuasive to remove the rejection. Applicant's arguments are the same as those made with respect to Ahmed et al. in view of Staniforth above, and are not found to be persuasive for the same reasons. Therefore the rejection is deemed proper and maintained.

Claims 11 and 35-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ahmed et al. (PCT international publication WO99/06025, reference of record in previous action) in view of Staniforth (PCT international publication WO97/03649, of record in previous action) as applied to claims -3, 6-10, 14-30 , 40-42, and 44-48 above, and further in view of Chickering et al. (US pre-grant publication 2004/0121003, cited in previous action)

The disclosure of Ahmed et al. in view of Staniforth is discussed above. Ahmed et al. in view of Staniforth does not disclose a method wherein the particles of heparin are jet milled at an inlet pressure of 0.1-3 bar or 2-12 bar, or wherein at least 90% by volume of the active particles are less than 20 μm in diameter prior to jet milling.

Chickering et al. discloses a method for making a dry powder blend comprising jet milling particles of a pharmaceutical active agent with larger particles of an excipient. (p. 1 paragraph 0009) Excipient particles are preferably 40-100 μm in diameter and can include sugars and amino acids, such as lactose, mannitol, leucine, or cysteine. (pp. 1-2, paragraph 0010) The microparticles to be jet milled can be formed by spray drying. (p. 2 paragraph 0013) The process substantially maintains the size and morphology of the individual microparticles while deagglomerating them. The jet mill can be operated at any pressure between 0 and 10 bar. (p. 10 paragraph 0130)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the jet milling procedure of Chickering et al. to prepare a particle blend as described by Ahmed et al. in view of Staniforth. One of ordinary skill in the art would have been motivated to use this method because Chickering et al. already discloses that the method is useful for making a blend of fine active particles with carrier particles. One of ordinary skill in the art would have reasonably expected success because jet milling is already known in the art as a routine method of making pharmaceutical powders.

With regard to the initial particle size listed in instant claim 39, one of ordinary skill in the art would have recognized that since the jet milling process substantially

preserves the size of individual particles, the active particles used in this process should already be of the desired size, which is much less than 20 µm.

Therefore the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted September 18, 2009, with respect to the above ground of rejection, have been fully considered and not found to be persuasive to remove the rejection. Applicant's arguments are the same as those made with respect to Ahmed et al. in view of Staniforth above, and are not found to be persuasive for the same reasons. Therefore the rejection is deemed proper and maintained.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ahmed et al. (PCT international publication WO99/06025, reference of record in previous action) in view of Staniforth (PCT international publication WO97/03649, of record in previous action) as applied to claims 1-3, 6-10, 14-30 , 40-42, and 44-48 above, and further in view of Stossel et al. (US patent 5464817, cited in previous action)

The disclosure of Ahmed et al. in view of Staniforth is discussed above. Ahmed et al. in view of Staniforth does not disclose a composition comprising rhDNAse.

Stossel et al. discloses a method of disaggregating actin, reducing the polymerization of free actin, and inhibiting the binding of actin to DNAse I, said method comprising administering an actin binding compound to the respiratory tract of a subject. (column 5 lines 45-65) This method can include addition of exogenous DNAse (column

6 lines 47-51) or preferably gelsolin or thymosin β4. (column 12 lines 29-34) Diseases treatable in this manner include various pulmonary diseases such as cystic fibrosis, chronic bronchitis, mucopurulent or purulent exacerbation of simple mucoid bronchitis, bronchorrhea, bronchopneumonia, widespread bronchiolitis, purulent pneumonia, pneumonic-alveolar-consolidation, asthma, with or without asthmatic bronchitis with mucus plugging, acute and/or chronic purulent sinusitis, empyema, bronchiectasis, bronchocoele, adult respiratory distress syndrome (ARDS), post-transplantation obliterative bronchiolitis, and allergenic bronchiolitis (fibrosing alveolitus), for example. (column 7 lines 11-21) These drugs can be administered by inhalation. (column 10 lines 62-67)

It would have been obvious to one of ordinary skill in the art at the time of the invention to add gelsolin or thymosin β4 to the therapeutic compositions of Ahmed et al. in view of Staniforth One of ordinary skill in the art would have been motivated to make the combination because Stossel et al. discloses these compounds to be useful for treating the same indications as the compounds of Ahmed et al., namely pulmonary diseases such as asthma. One of ordinary skill in the art would reasonably have expected success because combining two known prior art compositions known to be useful for the same purpose is well within the ordinary and routine level of skill in the art.

Therefore the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted September 18, 2009, with respect to the above ground of rejection, have been fully considered and not found to be persuasive to remove the rejection. Applicant's arguments are the same as those

made with respect to Ahmed et al. in view of Staniforth above, and are not found to be persuasive for the same reasons. Therefore the rejection is deemed proper and maintained.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ahmed et al. (PCT international publication WO99/06025, reference of record in previous action) in view of Staniforth (PCT international publication WO97/03649, of record in previous action) as applied to claims -3, 6-10, 14-30 , 40-42, and 44-48 above, and further in view of Trofast. (US patent 6027714, of record in previous action)

The disclosure of Ahmed et al. in view of Staniforth is discussed above. Ahmed et al. in view of Staniforth does not disclose a composition comprising mannitol or glucose.

Trofast discloses a composition for inhalation comprising budesonide and a carrier substance. (column 1 lines 23-28) The carrier substance is preferably a saccharide such as glucose or a sugar alcohol such as mannitol. (column 1 lines 34-39)

It would have been obvious to one of ordinary skill in the art to use glucose or mannitol as an inert powder carrier in the compositions of Ahmed et al. in view of Staniforth One of ordinary skill in the art would have been motivated to use these specific carriers because Trofast already discloses that they are useful as inert carriers for inhalable dry powders. One of ordinary skill in the art would reasonably have

reasonably expected success because Ahmed et al. already disclose that any conventional inert carrier substance can be used in the disclosed compositions.

Therefore the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted September 18, 2009, with respect to the above ground of rejection, have been fully considered and not found to be persuasive to remove the rejection. Applicant's arguments are the same as those made with respect to Ahmed et al. in view of Staniforth above, and are not found to be persuasive for the same reasons. Therefore the rejection is deemed proper and maintained.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERIC S. OLSON whose telephone number is (571)272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S Olson/
Examiner, Art Unit 1623
9/23/2009